REMARKS

Status of the Claims

Claims 23, 25-27, 30-34, 36, 39, 40, 42-48, 50-56 and 62-67 were in the application.

Claims 23, 25-27, 30-34, 36, 39, 40, 42-48, 50-56 and 62-67 have been rejected.

By way of this amendment, new claims 68-77 have been added.

Upon entry of this amendment, claims 23, 25-27, 30-34, 36, 39, 40, 42-48, 50-56 and 62-77 will be pending.

Summary of Amendment

New claims 68-77 have been added to refer to specific embodiments of the present invention. Support for the new claims is found throughout the specification and claims as originally filed.

No new matter has been added.

Claim Rejections – 35 U.S.C. § 103

Trouet in view of Houghten, Hussain, and Gluck and if necessary Guzman-Verduzco

Claims 23, 25-27, 30, 32-34, 42-43, 45-48, 50-56, and 62-67 stand rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Trouet et al (PNAS 79: 626-629 (1982) in view of Houghten (WO 84/02700), Hussain et al (EP 0341661), and Gluck (U.S. Patent 6,040,167), and if necessary Guzman-Verduzco (Molec Med 4(2):253-64 1990).

Trouet discloses the use of linkers that can be cleaved by lysosome enzymes in conjugates of non-peptide drugs to peptides in order to provide selective targeting of anti-tumor drugs without reducing toxicity of the drugs.

Houghten discloses the preparation of synthetic ST peptides and their use as immunogens in vaccines against enterotoxigenic strains of *E. coli* to protect an individual from intestinal colonization by such bacteria and the acute diarrhea and intestinal stress caused thereby.

Hussain discloses the addition of a non-peptide carrier molecule to improve uptake and bioavailability of drugs delivered into mucosal tissue.

Gluck discloses liposomes that comprise receptor binding peptides and proteins

Guzman-Verduzco discloses conjugates comprising ST and LT enterotoxins.

The Office asserts that it would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to make a composition comprising an ST receptor binding ligand and a non peptide radiostable cytotoxic or cytostatic agent, as well as using liposomes vesicles to deliver various drugs of interest. The Office asserts that the it would have been obvious to make a pharmaceutical composition as claimed because Hussain et al. and Trouet et al, and if necessary Guzman et al. teach using proteins and peptides for drug delivery and that a person of ordinary skill in the art would have a reasonable expectation of success since Houghton, Hussain and Trouet (and/or Guzman) demonstrated success in generating compositions having peptide and non-peptide agents. Additionally, the Office asserts that one skilled in the art would have a reasonable expectation of success because Gluck demonstrated the use of liposomes vesicles that comprise receptor binding peptides and proteins. Applicant respectfully disagrees.

Applicant respectfully asserts that the combination of references does not establish a prima facie case of obviousness. Applicant respectfully notes that Houghton was mischaracterized or misinterpreted in the Official Action. When the references are properly construed, one skilled in the art would not modify the teachings of Trouet with those of Houghton and the other references to produce the claimed invention.

Houghton teaches producing a vaccine useful to induce immune responses against bacterial enterotoxins. Houghton states on page 15 that the ST antigens used in the vaccine could be prepared to have several times the immunogenicity and substantially less biological activity as the "native toxin". Houghton discloses conjugating ST peptide to itself, to the heat labile enterotoxin LT and to immunoglobulin. Applicants note that LT toxin is a peptide and it is not a cytotoxin. LT is referred to as a toxin because it is produced by bacteria and when it binds to cellular receptors in the gut the cells release water causing diarrhea. The diarrhea leads to the death of the individuals. The toxins do not the kill the cells. They are not cytotoxic.

Combining the ST peptide disclosed in Houghten with a cytotoxic/cytostatic agent would be contrary to the purpose of Houghten. The Office's assertion on page 11 of the Official Action that "the ST peptide of the Houghten reference is in itself a toxin/cytotoxin/enterotoxin" is not

accurate. ST peptide and LT peptide are referred to as toxins or enterotoxins but they are not cytotoxins. The toxicity of the ST and LT enterotoxins is not the induction of cell death but the induction of abnormally high levels of fluid and electrolyte secretion by intestinal cells, leading to severe diarrhea, dehydration and in some cases death. Houghten's purpose for making multimers is to provide an antigen that is immunogenic compared to native toxin. Houghten's purpose is not to kill cells that come into contact with the antigens. In fact, Houghten would want to avoid killing immune cells involved in generating an immune response against the antigen that may come into contact with the antigen. Houghten intends to induce immune responses and would not target immune cells with death.

While Trouet discloses linking cancer drugs to targeting molecules, Trouet would not use ST peptides taught by Houghten. None of Trouet, Houghton, Hussain, Gluck or Guzman-Verduzco teaches or suggests conjugating ST peptides to cytostatic or cytotoxic agents. Houghten discloses inducing immune responses against the ST antigen that would prevent ST antigen released by bacteria from stimulating the secretion of electrolytes and fluid. Houghten teaches administering ST peptide to induce an immune response against a protein made by infectious bacteria. One skilled in the art would not use the teaching of any of Houghton, Hussain, Gluck or Guzman-Verduzco to modify Trouet to produce an ST peptide linked to a cytotoxin.

In addition to rendering Houghten unsatisfactory for its intended use, one skilled in the art would not otherwise combine the references to produce the claimed invention. The invention is not obvious under the law of obviousness as articulated in KSR International Co. v. Teleflex Inc., 82 USPQ2d 1385 (2007). The decision in KSR supports a conclusion that the invention is not obvious. In KSR, the US Supreme Court reasoned that an invention is obvious

> if a technique has been used to improve one device, and a person of ordinary skill in the art would recognize that it would improve similar devices in the same way…

KSR at 1396 . In the instant case, the vaccines in Houghten are not similar products to those of Trouet, and the ST antigen in Houghten is being used as an immunogen with a different purpose than in a conjugate that comprises cytotoxic agents as taught by Trouet.

One skilled in the art would not conclude that the claimed invention is prima facie obvious in view of the combination of Trouet in view of Houghten, Hussain and Gluck, and if necessary Guzman-Verduzco. Applicant respectfully requests that the rejection of claims 23, 25-27, 30, 32-34, 42-43, 45-48, 50-56, and 62-67 under 35 U.S.C. § 103(a) as allegedly unpatentable over Trouet in view of Houghten, Hussain and Gluck, and if necessary Guzman-Verduzco be withdrawn

Trouet in view of Houghten, Hussain, and Gluck and if necessary Guzman-Verduzco

Claims 23, 25-27, 30-34, 40, 42-43, 45-48, 50-56, and 62-67 stand rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Trouet et al (PNAS 79: 626-629 (1982) in view of Houghten (WO 84/02700), Hussain et al (EP 0341661), and Gluck (U.S. Patent 6,040,167), and if necessary Guzman-Verduzco (Molec Med 4(2):253-64 1990), and further in view of Lee et al. (US. 5,183,805).

Trouet, Houghten, Hussain, Gluck and Guzman-Verduzco are discussed above.

Lee discloses conjugating EGF peptides to chemotherapeutics such as 5-fluorouracil.

For the same reasons set forth above, Applicant respectfully asserts that the combination of references does not establish a prima facie case of obviousness. One skilled in the art would not modify the teachings of Trouet with those of Houghton and the other references to produce the claimed invention.

As set forth above, Houghton teaches producing a vaccine useful to induce immune responses against bacterial enterotoxins including conjugating ST peptide to itself, to the heat labile enterotoxin LT and to immunoglobulin. The LT toxin is a peptide and it is not cytotoxic. Combining the ST peptide with a cytotoxic/cytostatic agent would be contrary to the purpose of Houghten. Houghten's purpose for making multimers is to provide an antigen that is more immunogenic compared to native toxin. Houghten's purpose is not to induce immune cells to generate an immune response against the antigen, not to kill the cells which may come into contact with it.

Trouet would not use ST peptides taught by Houghten. None of Trouet, Houghton, Hussain, Gluck or Guzman-Verduzco teaches or suggests conjugating ST peptides to or using ST

peptides with non-peptide, radiostable cytostatic or cytotoxic agents as set forth in the claims. One skilled in the art would not use the teaching of any of Houghton, Hussain, Gluck or Guzman-Verduzco to modify Trouet to produce an ST peptide linked to a cytotoxin. Using the teachings of Houghten as applied in the rejection is contrary to the intended use.

Moreover, one skilled in the art would not combine the references to produce the claimed invention. Under KSR, the fact that the references collectively teach all of the elements of the claim does not by itself establish in a prima facie case of obviousness. In the instant invention, the vaccines in Houghten are not similar products to those of Trouet, and the ST antigen in Houghten is being used as an immunogen with a different purpose than in a conjugate that comprises cytotoxic agents as taught by Trouet.

Lee provides no additional teachings that would make up for this deficiency in establishing a prima facie case.

One skilled in the art would not conclude that the claimed invention is prima facie obvious in view of the combination of Trouet in view of Houghten, Hussain and Gluck, and if necessary Guzman-Verduzco and further in view of Lee. Applicant respectfully requests that the rejection of claims 23, 25-27, 30-34, 40, 42-43, 45-48, 50-56, and 62-67 under 35 U.S.C. § 103(a) as allegedly unpatentable over Trouet in view of Houghten, Hussain and Gluck, and if necessary Guzman-Verduzco be withdrawn

Double Patenting Rejection

Claims 23, 25-28, 33, 34, 38 and 40 have been rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 2, 5 and 6 of U.S. Patent No. 5,962,220.

Claims 23, 25-28, 33, 34, 38 and 40 have been rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-4, 7-10 and 13 of U.S. Patent No. 6,087,109.

Claims 23 and 28 have been rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-24, 26, 28, 29 and 33-41 of U.S. Patent No. 7,097,839.

Applicant provides herewith Terminal Disclaimer documents as applied to the claims are rejected.

Claims 23, 25-27, 48, 50, 51, 52, 54 and 55 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 10, 12 and 15-17 and 20-22 of copending Application No. 11/494,901 (US 20060269477). Although the conflicting claims are not identical, they are not patentably distinct from each other because the claimed invention in the '901 application reads on the instant claimed invention.

This rejection is provisional. As the co-pending application has not yet issued, no action is required at this time.

Conclusion

Claims 23, 25-27, 30-34, 36, 39, 40, 42-48, 50-56 and 62-77 are in condition for allowance. A notice of allowance is earnestly solicited.

The Commissioner is hereby authorized to charge any deficiencies of fees and credit of any overpayments to Deposit Account No. 50-0436.

Respectfully Submitted,

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